SnapShot: Sirtuins, NAD, and Aging

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Cell Metabolism

TARGETS OF SIRTUINS

nucleus cytoplasm mitochondria

SIRT6

cMyc	CtIP
H3K9	GCN5
H3K56	SNF2H
HIF1α	G3BP
NF-κB	FoxO3
TNFα	PARP1
SREBP1/2	

SIRT1

H3K9	HDAC1	PPARα	HNF4α	Rb	TFAM	eNOS	Atg7
H3K56	PGC1α	PPARγ	HIF1α	NBS1	NF-κB	LKB1	Atg8
H4K16	FoxO1	LXR	HIF2α	XPA	MyoD	Smad7	14-3-3ζ
H1K26	FoxO3a	FXR	PARP1	WRN	Nhlh2	β-catenin	PGAM1
Suv39h1	Foxa2	RARβ	p53	CREB	cMyc	Survivin	AceCS1
p300	CRTC1	SREBP1c	Ku70	Nkx2-1	UCP2	Akt	PTP1B
PCAF	CRTC2	SREBP2	E2F1	STAT3	TSC2	Atg5	S6K1

SIRT7

cMyc	CUL4B
H3K18	ELK4
PAF53	RNA Pol I
HIF1α	Mybbp1a
HIF2α	TFIIIC2
DCAF1	mTOR
DDB1	p53

SIRT4

GDH
MCD
IDE
SLC25A5

SIRT3

LCAD	AceCS2	OTC
VLCAD	GDH	CypD
HMGCS2	IDH2	OPA1
NDUFA9	MRPL10	PDH
Skp2	PDP1	FoxO3
SDHA	SOD2	

SIRT5

CPS1
HMGCS2
PDH
SDH
SOD1

SIRT2

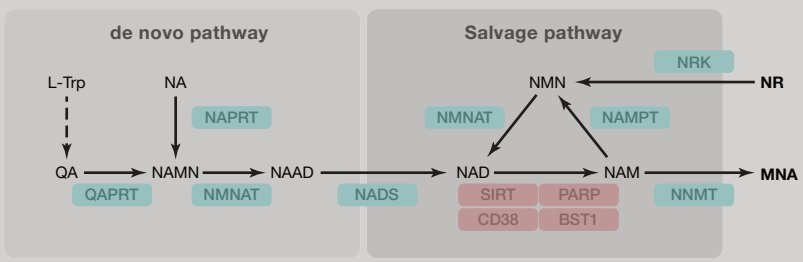
H4K16	NF-κB
H3K56	HIF1α
H3K18	CDK9
FoxO1	Cdc20
FoxO3a	APC
p300	

SIRT2

Tubulin	Keratin8
G6PD	PRLR
LDH	MEK1
PEPCK1	ITPK1
ACYL	S6K1
Par3	

	Enzymatic Activities	Physiological Functions
SIRT1	Deacetylase ADP-ribosylase (weak)	SIRT1 orthologs extend life span in yeast, worms, flies, and mice. SIRT1 also protects against metabolic disorders, such as obesity, insulin resistance, and hepatic steatosis, as well as aging-related neuronal diseases, by deacetylating histones and many transcription factors and cofactors.
SIRT2	Deacetylase	SIRT2 primarily resides in cytoplasm but also relocates to nucleus upon stress and during mitosis. Nuclear SIRT2 deacetylates histones and various transcription factors and regulates cell-cycle progression and cell differentiation. SIRT2 also regulates various metabolic enzymes in the cytosol.
SIRT3	Deacetylase	The major mitochondrial deacetylase SIRT3 affects acetylation of hundreds of mitochondrial proteins and regulates many metabolic enzymes through deacetylation, including LCAD (β-oxidation). SIRT3 KO mice develop hepatic steatosis and insulin resistance on high-fat diet. SIRT3 also acts as a tumor suppressor by reducing ROS and its loss reprograms cellular metabolism in various human cancers.
SIRT4	Deacetylase (malonyl CoA decarboxylase) ADP-ribosylase	SIRT4 is involved in amino acid metabolism by ADP-ribosylating GDH. SIRT4 KO mice manifest hyperinsulinemia due to the constitutive activation of GDH. SIRT4 is also a tumor suppressor and regulates glutamine metabolism in cancer cells via GDH. SIRT4 KO mice are prone to lung cancer.
SIRT5	Deacylase (Succinyl, malonyl, glutaryl groups) Deacetylase (weak)	Loss of SIRT5 leads to hypersuccinylation and malonylation of mitochondrial proteins and inhibition of β-oxidation and ketogenesis. SIRT5 KO mice also manifest elevated ammonia level due to the lack of CPS1 activation during fasting.
SIRT6	Deacylase (long-chain fatty acyl groups) Deacetylase (weak) ADP-ribosylase (weak)	Overexpression of SIRT6 extends life span in mice. Deletion of SIRT6 results in hypoglycemia and aging-like phenotypes in mice, including lymphopenia, kyphosis, and loss of fat pads. SIRT6 has various roles in transcription, genome stability, and metabolic regulation. SIRT6 efficiently removes long-chain fatty acids from lysine and thus promotes TNFα secretion. SIRT6 acts as a corepressor for HIF-1α and cMYC and, thus, inhibits tumorigenesis.
SIRT7	Deacetylase	In cancer cells, SIRT7 deacetylates H3K18 and represses the transcription of tumor-suppressor genes. SIRT7 is also involved in lipid metabolism, and SIRT7 KO mice are resistant to diet-induced obesity and fatty liver.

NAD METABOLISM



Enzymes	Physiological functions
Nampt	Insulin secretion, Circadian rhythm, Cancer metabolism
Nmnat1	Leber congenital amaurosis Wallerian degeneration
Nmnat2	Axonal development Protection from axonal injury
Nmnat3	Hemolytic anemia Protection from axonal injury
NNMT	Obesity, Tumorigenesis Longevity in *C. elegans*
CD38	Immune response Oxytocin secretion

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Cell Metabolism

The yeast SIR2 gene was initially found to slow aging, and this protein and the mammalian ortholog SIRT1 were soon shown to function as NAD-dependent deacetylases that alter activities of their substrate proteins. SIR2 orthologs slow aging in multiple species. The seven mammalian sirtuins show homology across their catalytic and NAD-binding domains. These proteins have various deacylase activities in addition to deacetylation, including the removal of succinyl, malonyl (SIRT5), and long-chain fatty acid acyl esters (SIRT6) from lysines. Substrates of nuclear sirtuins include histones but also nuclear transcription factors and cofactors. In addition, all seven sirtuins deacylate many metabolic enzymes. In particular, mitochondrial sirtuins play key roles in deacylating and activating enzymes involved in fatty acid oxidation, the TCA cycle, and other oxidative pathways. Of note, SIRT3 is the only known mitochondrial deacetylase and confers neuroprotection.

Physiological Effects of Deacetylation by Sirtuins

One major outcome is the repression of glycolytic metabolism and the activation of oxidative metabolism. This includes activation of mitochondrial defense systems against reactive oxygen species and protein unfolding. This metabolic strategy is accentuated when energy is limiting, for example on a diet of calorie restriction (CR).

It was reported by some labs that SIR2 may not be necessary for the effects of CR in yeast. Technical reasons might account for these lab-to-lab differences, which may include variations in CR conditions or strain-specific differences. In mammals, the case that sirtuins mediate effects of CR is very strong, since sirtuins are activated by this diet and their absence abolishes many effects of CR, including longevity.

A very interesting recent development in the field is that the NAD cosubstrate may play an important role in aging since NAD levels decline with aging in many organisms leading to a decline in sirtuins' activities. Importantly, supplementation with NAD precursors can ameliorate or reverse the effects of aging in old mice or worms. The reasons underlying the decline in NAD with aging are not fully understood, but PARP-1 inhibition prevents NAD depletion, suggesting that accumulating nuclear DNA damage and PARP activation in aged animals may play a role in NAD depletion. Another possibility stems from the fact that the circadian clock drives NAD synthesis (and thus sirtuins' activities), and the robustness of the clock declines with aging, perhaps leading to reduced NAD synthesis.

Impact of Sirtuin Biology on Human Health

First, several small molecule activators have been developed for SIRT1 and mitigate many of the diseases that are also improved by CR (diabetes, inflammation, cancer, cardiovascular disease, or osteoporosis). Since NAD levels fall with normal aging, supplementation with NAD precursors to restore "youthful" NAD levels may also offer a strategy to slow the effects of aging. Indeed, NAD supplementation and SIRT1 activation may well provide synergistic effects. Second, SIRT3, SIRT4, or SIRT6 may help drive cancer cell metabolism, since loss of SIRT3 or SIRT6 favors glycolytic metabolism (the Warburg effect) and loss of SIRT4 promotes glutamine metabolism, both hallmarks of tumor cells. Indeed, roughly 20%–40% of numerous human tumors show gene loss of otherwise reduced expression of SIRT3, SIRT4, or SIRT6.

Future Directions

Sirtuins also link metabolism, NAD, and the potential to affect gene expression by histone deacetylation. It will be important to study whether the environment (diet, stress, or exercise) impacts on the status of the epigenome via sirtuins. Such an interaction could provide an immediate link between lifestyle and physiology, perhaps influencing human health. Such effects on the epigenome may perdure, i.e., in the known effects of maternal environment during gestation on the health of the progeny. We may hope to find new ways of treating conditions in children or adults arising from epigenetic effects occurring in utero.

In summary, sirtuins are a unique class of NAD-dependent deacylases with many roles in cellular metabolism, health, and aging. It will be fascinating to follow how pharmacological approaches targeting sirtuin activities or the levels of NAD can be harnessed to improve human health.

ABBREVIATIONS

CtIP, CtBP-interacting protein; G3BP, RNA-binding Ras-GAP SH3 binding protein; CRTC, CREB-regulated transcription coactivator; PPAR, peroxisome proliferator-activated receptor; RARβ, retinoic acid receptor β; PARP1, poly (ADP-ribose) polymerase 1; LXR, liver X receptors; FXR, farnesoid X receptor; HNF4α, hepatocyte nuclear factor 4α; HIF, hypoxia inducible factor; NBS1, Nijmegen breakage syndrome 1; XPA, xeroderma pigmentosum, complementation group A; WRN, Werner syndrome, RecQ helicase-like; CREB, cAMP responsive element binding protein: TFAM, transcription factor A, mitochondrial: Nhlh2, nescient helix loop helix 2; PGAM1, phosphoglycerate mutase 1; AceCS, acyl-CoA synthetase; PTP1B, protein tyrosine phosphatase 1B; Mybbp1a, Myb-binding protein 1a; TFIIIC2, general transcription factor IIIC, polypeptide 2; GDH, glutamate dehydrogenase; MCD, malonyl-CoA decarboxylase; IDE, insulin-degrading enzyme; VCAD, long-chain Acyl-CoA dehydrogenase; VLCAD, very long-chain Acyl-CoA dehydrogenase; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; NDUFA9, NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 9; Skp2, S phase kinase-associated protein 2; SDHA, succinate dehydrogenase complex, subunit A; IDH2, isocitrate dehydrogenase 2; MRPL10, mitochondrial ribosomal protein L10; PDP1, pyruvate dehyrogenase phosphatase catalytic subunit 1; SOD, superoxide dismutase; CypD, cyclophilin D: OTC, ornithine carbamoyltransferase; OPA1, optic atrophy 1; PDH, pyruvate dehydrogenase; CPS1, carbamoyl-phosphate synthase 1; G6PD, glucose-6-phosphate dehydrogenase; LDH, lactate dehydrogenase; PEPCK1, phosphoenolpyruvate carboxykinase; ACYL, ATP citrate lyase; PRLR, prolactin receptor; MEK1, mitogen-activated protein kinase 1; ITPK1, inositol-tetrakisphosphate 1-kinase; S6K1, ribosomal protein S6 kinase polypeptide 1; Nampt, nicotinamide phosphoribosyltransferase; Nmnat, nicotinamide mononucleotide adenylyltransferase; NAPRT, nicotinic acid phosphoribosyltransferase; QAPRT, quinolinic acid phosphoribosyltransferase; NADS, NAD synthetase; NNMT, nicotinamide N-methyltransferase; NRK, nicotinamid riboside kinase; L-Trp, L-tryptophan: NA, nicotinic acid; QA, quinolic acid; NAMN, nicotinic acid mononucleotide; NAAD, nicotinic acid adenine dinucleotide; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; MNA, 1-methylnicotinamide.

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